Citation:

Dowd JB, Aiello AE. Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? *Int J Epidemiol*. 2008; 37 (5): 1,059-1,066.

PubMed ID: 18456713

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the impact of the 1998 US Food and Drug Administration (FDA) folic acid fortification policy on disparities in folate status among the US population.

Inclusion Criteria:

- Data were taken from three waves of the National Health and Nutrition Examination Surveys (NHANES):
  - The second phase of NHANES III (1991-1994)
  - NHANES surveys (1999 to 2000 and 2001 to 2002)
- Adults in NHANES surveys were 25 years of age and older.

Exclusion Criteria:

The study excluded data from the first phase of NHANES III (1988 to 1991) in order to exclude the before-and-after time frame not close to implementation of the folic acid fortification policy.

Description of Study Protocol:

Recruitment

Nationally representative data from three waves of the National Health and Nutrition Examination Surveys (NHANES):

- Thesecond phase of NHANES III (1991 to 1994)
- NHANES surveys (1999 to 2000 and 2001 to 2002)

People surveyed were civilian, non-institutionalized population of the US two months of age and older.

Design

National population-based health and nutrition survey.

Dietary Intake/Dietary Assessment Methodology

Red blood cell (RBC) folate: Blood samples were collected using venipuncture. RBC folate was tested using two methods:

- Before November 1993, the samples were assayed by the Quanta Phase I Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, USA)
- From December 1993, they were assayed by the Quanta Phase II Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, US).

CDC provided a correction factor for calibration.

Blinding Used

RBC folate was examined by laboratories.

Intervention

Folic acid fortification policy.

Statistical Analysis

- Crude absolute differences in prevalence and relative prevalence ratios were used to calculate across income quartiles and race/ethnic groups
- Multivariable Poisson regression model:
    - Used to calculate the prevalence ratio
    - Used to adjust absolute differences for low RBC folate status by income quartile and race/ethnicity, adjusted for age and sex
- Kernel density estimates were used to examine smoothed distributions of continuous RBC folate by income groups and race/ethnicity before and after fortification
- Relative and absolute concentration curves and indices for income were determined by plotting the cumulative proportion of the sample ranked by income quartile on the X-axis against the cumulative proportion of cases of low RBC folate status on the Y-axis
- All analyses: STATA version 10.0 adjusting for complex survey design.

Data Collection Summary:

Timing of Measurements

NHANES research conduced between 1991 and 1994 (pre-fortification period) and surveys completed in 1999 to 2000 and 2001 to 2002 (post-fortification period).

Dependent Variables

- RBC folate: Blood samples were collected using venipuncture. RBC folate was tested using two methods:
  - Before November 1993, assayed by the Quanta Phase I Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, US)
  - From December 1993, assayed by the Quanta Phase II Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, US)
- RBC folate: Used a cut-point of less than 362.6nmol (160mcg per L) to group the folate values into two groups.

Independent Variables

The implementation of folic acid fortification by January, 1998.

Control Variables

- Age
- Gender
- Income: Divided into four quartiles based on the poverty income ratio (PIR), with PIR being the ratio of a family's income to their appropriate threshold income based on household size
- Race-ethnicity: Non-Hispanic whites, non-Hispanic black and Mexican-American.

Description of Actual Data Sample:

- *Initial N:* Repeated cross-sectional data from the US NHANES:

	Participants	Missing Data for RBC	Missing Data for Income
NHANES (1991 to 1994)	8,342	357 (4%)	671 (8%)
NHANES (1999 to 2000 and 2001 to 2002)	8,252	262 (3%)	804 (10%)

- *Attrition (Final N):* The final samples consisted of 7,671 individuals in NHANES III (1991 to 1994) and 7,288 individuals in the combined NHANES (1999 to 2000 and 2001 to 2002 surveys)
- *Age:* 25 years and older
- *Ethnicity:* Non-Hispanic whites, non-Hispanic black and Mexican-American
- *Location:* United States.

Summary of Results:

- Following fortification, the prevalence of low folate status dropped from 528 to 110 out of 1,000 for the lowest income quartile, and from 374 to 42 out of 1,000 in the highest income quartile
- The prevalence of low folate status in non-Hispanic blacks dropped from 647 out of 1,000 to 171 out of 1,000 following fortification; for Hispanics it fell from 484 out of 1,000 to 58 out of 1,000 and for non-Hispanics whites the risk fell from 327 out of 1,000 to 38 out of 1,000
- Adjusted for age, sex, race/ethnicity and income quartile based on a Poisson regression model, the prevalence of low RBC folate (less than 362.6nmol) pre- and post-folic acid fortification by race/ethnicity and income quartile are showed in Table 2.

Table 1. Distribution of Cases of Low RBC Folate (Less than 362.2nmol per L) by Income and Race/Ethnicity Before and After Fortification, National Health and Nutrition Examination Survey 1991 to 1994 and 1999 to 2001, United States, Ages 25 and Older

	Rate per 1,000 (95% CI)	Excess Prevalence per 1,000 (95% CI)	Crude Relative Ratio (95% CI)
Income			
Pre-fortification (1991 to 1994)			
Bottom income quartile	528 (507 to 549)	155 (124 to 186)	1.41 (1.32 to 1.52)
Third income quartile	496 (472 to 520)	123 (90 to 156)	1.33 (1.23 to 1.44)
Second income quartile	442 (418 to 467)	69 (36 to 102)	1.18 (1.09 to 1.29)
Top income quartile	374 (351 to 396)	0	1
Post-fortification (1999-2001)			
Bottom income quartile	110 (91 to 128)	67 (47 to 87)	2.59 (2.01 to 3.32)
Third income quartile	93 (79 to 107)	51 (35 to 66)	2.19 (1.73 to 2.79)
Second income quartile	59 (48 to 69)	16 (3 to 29)	1.38 (1.07 to 1.79)

Top income quartile	42 (34 to 50)	0	1
Race/ethnicity			
Pre-fortification (1991 to 1994)			
Non-Hispanic black	647 (626 to 667)	320 (293-346)	1.98 (1.86-2.10)
Hispanic	484 (461 to 507)	158 (129-186)	1.48 (1.38-1.59)
Non-Hispanic white	327 (310 to 344)	0	1
Post-fortification (1999 to 2001)			
Non-Hispanic black	171 (152 to 190)	134 (114 to 153)	4.54 (3.76 to 5.50)
Hispanic	58 (48 to 67)	20 (9 to 31)	1.53 (1.22 to 1.92)
Non-Hispanic white	38 (32 to -44)	0	1

Table 2. Adjusted Relative and Absolute Differences in Prevalence of Low RBC Folate (Less than 362.6nmol) Pre- and Post-folic Acid Fortification by Race/Ethnicity and Income Quartile, National Health and Nutrition Examination Surveys, 1991 to 1994 and 1999 to 2002*

	Pre-fortification (1991 to 1994) **Prevalence Ratio (95% CI)**	**Post-fortification (1999-2002)** **Prevalence Ratio (95% CI)**	**Pre-fortification (1991-1994)** **Absolute Difference (per 1,000) (95% CI)**	**Post-fortification (1999-2002)** **Absolute Difference (per 1,000) (95% CI)**
White	Reference	Reference	Reference	Reference
Black	1.64 (1.42 to 1.89)	3.75 (2.83 to 4.98)	233 (180 to 286)	121 (96 to 146)
Hispanic	1.21 (0.99 to 1.49)	1.18 (0.89 to 1.76)	73 (-13 to 160)	8 (-9 to 26)
Top income quartile	Reference	Reference	Reference	Reference
Second income quartile	1.12 (1.01 to 1.23)	1.28 (1.0 to 1.64)	48 (15 to 80)	6 (-4 to 18)
Third income quartile	1.22 (1.09 to 1.37)	2.07 (1.59 to 2.71)	89 (46 to 133)	36 (17 to 55)
Bottom income quartile	1.27 (1.12 to 1.43)	2.08 (1.60 to 2.70)	124 (77 to 170)	41 (20 to 61)

Observations 7,671	7,288	7,671	7,288	

* Adjusted for age and gender.

Other Findings

Figures showed:

- Income and racial/ethnic differentials in low folate status remained following fortification
- Low RBC folate status became relatively more concentrated among the poor following fortification (179% increase in the Relative Concentration Index [RCI])
- The Absolute Concentration Index (ACI) decreased by 53.9%, which indicated the dramatic decreases in low RBC folate status for all income groups.

Author Conclusion:

- The effects of the fortification policy highlighted the importance of distinguishing absolute from relative differences when evaluating interventions to reduce health disparities
- Targeting of high-risk populations was likely needed to eliminate remaining folate disparities.

Reviewer Comments:

- *The study showed that all income and racial/ethnic groups in the US benefited in absolute terms from the FDA-mandated folic acid fortification policy, while individuals with low RBC folate status following fortification were more concentrated in groups with lower income and non-Hispanic black race*
- *The study did not examine changes in dietary or supplement intake by subgroup that might contribute to changes in folate disparities over the time period examined*
- *The study only had a one-time measurement of economic status such as income, which may be measured with error and not reflect broader dimensions of SES. This may underestimate the relationship between SES and folate status both before and after fortification.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	???
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes

10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes